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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,065	12/05/2001	Keith D. Allen	R-648	2751

7590 08/13/2003

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EXAMINER
BERTOGLIO, VALARIE E

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Acti n Summary	Application No. 10/010,065	Applicant(s) ALLEN ET AL.	
	Examiner Valarie Bertoglio	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-4,11-17 and 35-71* is/are pending in the application.

4a) Of the above claim(s) *1-4,11-17 and 35-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *12* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

Applicant's arguments filed 04/14/2003, paper number 12, have been fully considered. Claims 5-10 and 18-34 have been cancelled. Claims 57-71 have been added. Claims 1-4,11-17 and 35-56 have been withdrawn. Claims 1-4,11-17, 35-71 are pending and claims 57-71 are under consideration in the instant action.

Specification

Applicants arguments to the objection to the specification on the grounds that the specification is unclear as to the phenotype of the claimed mice with regard to fasting blood glucose levels has been considered and was not found persuasive. The statement on page 62, lines 28-30 of the specification, disclosing that heterozygous mutant mice display decreased fasting glucose levels is contradictory to the statement on page 59, line 12 disclosing that heterozygous mutant mice have increased fasting blood glucose levels. Figure 4 supports the statement that heterozygous mutant mice had increased blood glucose levels. Applicants respond that Table 2 does not refer to fasting glucose levels but non-fasting glucose levels. However, the relevance of this argument is unclear. Examiner's explanation of the lack of clarity of the specification with regard to the phenotype of the mouse did not rely on Table 2. Applicants' response also gives evidence that heterozygous mice display reduced serum non-fasting glucose levels (page 4, lines 24-29), however, they fail to address the fact that the specification states that "heterozygous mutant mice had increased fasting blood glucose levels." (page 59, line 12-page 60, line 1). With evidence in the specification to support contradictory phenotypes, it cannot be determined which phenotype(s) the mice actually displayed.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57-71 as newly added are rejected under 35 U.S.C 112, 1st paragraph as containing subject matter which was not described in the specification in such a way as to reasonably enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 5-10 and 18-34 have been cancelled and thus, the rejection as it pertains to claims 5-10 and 18-34 is withdrawn. The previous rejection is, however, applicable to claims 57-71 for the reasons of record advanced on pages 7 and 8 of the previous office action mailed 01/07/2003. For clarity, the rejection is reiterated below.

1) The specification fails to enable knocking out any glucagon receptor gene other than that set forth by SEQ ID NO:1 (see page 8, 2nd paragraph of prior office action mailed 01/07/2003).

By use of the phrase "an endogenous glucagon receptor gene", claims 57 and 70, are drawn to any glucagon receptor gene, including orthologues of the mouse glucagon receptor set forth by SEQ ID NO:1. The specification only teaches one mouse glucagon receptor gene (SEQ ID NO: 1; page 10, lines 6-8). The specification does not provide adequate guidance for determining other mouse glucagon receptor genes or that other glucagon receptor genes exist in mouse or have the same function as the glucagon receptor gene disclosed. Therefore, a knockout of any glucagon receptor gene other than the glucagon receptor described in the specification would have different phenotypic effects that are not predictable (see pages 5-6 of the prior office action). Deleting the word "an" preceding the term "endogenous" in claims 57 and 70 would overcome this rejection.

2) The specification fails to enable making mice comprising a homozygous and/or heterozygous disruption of the glucagon receptor gene wherein the mice exhibit any phenotype

(see page 5, paragraph 2; page 7, paragraph2; page 8, paragraph 1 of prior office action mailed 01/07/2003).

Claim 57 encompasses mice heterozygous for a disruption in the glucagon receptor gene wherein the mice have any phenotype. The phrase, "A transgenic mouse whose genome comprises a disruption in an endogenous glucagon receptor gene" encompasses both homozygous and heterozygous mice. The following phrase of the claim, "wherein where the disruption is homozygous, the transgenic mouse exhibits, relative to a wild-type mouse, a metabolic abnormality or a pancreatic abnormality" limits the recited phenotype to homozygous mice only. Therefore, the heterozygous mice encompasses by the claim have no recited phenotype and therefore, encompasses mice heterozygous for a disruption in the glucagon receptor gene wherein the mouse has any phenotype.

The specification teaches that mice heterozygous for a disruption in the glucagon receptor gene display both increased fasting blood glucose levels (sentence bridging pages 59-60) and decreased fasting glucose levels (page 62, lines 28-30), increased fasting insulin levels (Figure 11), reduced non-fasting serum glucose levels (page 59, line 2; Table 2) and mild to moderate hyperplasia and hypertrophy of the islet cells (page 56, lines 20-21). Therefore, the specification is enabling for heterozygous mice having only those phenotypes as described by the specification. As set forth in the art and described in said prior office action (page 5, paragraph 2), the phenotype of a transgenic animal was unpredictable at the time of filing. The specification does not overcome the unpredictability inherent in generating knockout mice such that any phenotype could be obtained and its use determined prior to learning the phenotype. The specification does not teach any phenotype for the claimed heterozygous mice other than those listed above. Without reciting a phenotype in claim 57 for the heterozygous mice, the claim encompasses heterozygous mice with other phenotypes not supported by the

specification. Without guidance as to how to obtain and use the heterozygous mice, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to obtain any phenotype in a mouse heterozygous for a disruption in the glucagon receptor gene or to use said mouse wherein the mouse has any phenotype.

Claim 70 encompasses a transgenic mouse whose genome comprises a homozygous disruption in an endogenous glucagon receptor gene wherein the mouse has any phenotype. There is no phenotype recited for the claimed mouse. The phenotype of reduced fertility recited in line 5 of the claim is the phenotype of the offspring of the claimed mouse and does not reflect any observable or detectable phenotype of the claimed mouse that correlates to the disruption in the glucagon receptor gene. The specification fails to overcome the unpredictability in the art as set forth above and in the prior office action. Accordingly, it would require one of skill in the art at the time the invention was made, undue experimentation to determine how to make and use the claimed mouse having any phenotype.

Claims 58-69 depend from parent claim 57 and also encompass both the homozygous heterozygous mice encompassed by the parent claim. Accordingly, the above rejection also applies to claims 58-69.

Claim 71 depends from parent claim 70 and also encompasses both the homozygous heterozygous mice encompassed by the parent claim. Accordingly, the above rejection also applies to claim 71.

Applicants argue that the rejections reiterated above are overcome by limitations introduced to newly added claims 57-71. This argument is not persuasive. Applicants' do not address how newly added claims 57 and 70 overcome the rejection to the broad genera of glucagon receptor genes encompassed by the phrase "an endogenous glucagon receptor". Applicants' also argue that the specification is fully enabling for the newly added claims as they

are limited to specific phenotypes. However, claim 57 is written such that it encompasses a heterozygous mouse exhibiting any phenotype. Claims 58-69 and 71 are dependent from claim 57 and encompass both heterozygous and homozygous mice wherein the mice have specific phenotypes. However, the phenotypes cited by claims 59-63, 65-69 are not supported by the specification. Furthermore, the homozygous mouse of claim 70 does have a phenotype. Therefore, applicants' arguments with respect to claims 57-71 are not persuasive the rejections reiterated above are maintained for the reasons of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

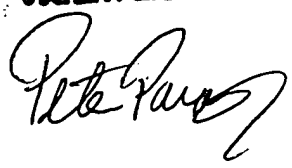
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on Mon-Weds 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for

the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

PETER PARAS
PATENT EXAMINER



Valarie Bertoglio
Examiner
Art Unit 1632